Title
Neuropsychological changes in efavirenz switch regimens.

Journal
AIDS, 33(8)

ISSN
0269-9370

Authors
Li, Yijia
Wang, Zheng
Cheng, Yu
et al.

Publication Date
2019-07-01

DOI
10.1097/qad.0000000000002206

Peer reviewed

HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

AIDS. 2019 July 01; 33(8): 1307–1314. doi:10.1097/QAD.0000000000002206.

Neuropsychological changes in efavirenz switch regimens

Yijia LI[1], **Zheng WANG**[2], **Yu CHENG**[2,3], **James T. BECKER**[3], **Eileen MARTIN**[4], **Andrew LEVINE**[5], **Leah H. RUBIN**[6], **Ned SACKTOR**[6], **Ann RAGIN**[7], and **Ken HO**[1,8]

[1]University of Pittsburgh School of Medicine, Pittsburgh, PA

[2]Department of Statistics, University of Pittsburgh, Pittsburgh, PA

[3]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA

[4]Rush University School of Medicine, Chicago, IL

[5]Department of Neurology, UCLA - David Geffen School of Medicine, Los Angeles, CA

[6]Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD

[7]Feinberg School of Medicine, Northwestern University, Chicago, IL

[8]Division of Infectious Diseases, Department of Medicine, University of Pittsburgh, Pittsburgh, PA.

Abstract

Background: Efavirenz is associated with side effects involving the central nervous system. However, it remains largely unknown whether switching off EFV improves neuropsychological performance.

Methods: We utilized data from the Multicenter AIDS Cohort Study (MACS). Participants were categorized by their use of EFV: never on EFV (No EFV), continuously on EFV (No Switch-OFF) and on EFV and then switched off (Switch-OFF). Baseline time points were defined as visits when first neuropsychological data were available. In Analysis 1, we compared neuropsychological and Center for Epidemiological Studies-Depression (CES-D) scores before and after EFV switch in Switch-OFF group, aligning participants at the time of switch. Analysis 2 evaluated trajectory of neuropsychological/CES-D score among the three groups.

Results: This analysis included 1,989 HIV-seropositive participants with neuropsychological data (1,675 in No EFV, 44 in No Switch-OFF, and 270 in Switch-OFF group). At baseline, participants had a median age of 37 years, median CD4 cell count 442 cells/μL, and 22.9% viral suppression rate. In Analysis 1, neuropsychological and CES-D scores did not show clinically significant changes over two years prior to and four years after switch in Switch-OFF group. In Analysis 2, trends in neuropsychological and CES-D scores in the three different groups did not show significantly differences during a median of 3.2 years of follow up.

Correspondence: Dr. Ken Ho, Falk Medical Building, 3601 Fifth Ave., Suite 3A Pittsburgh, PA 15213, Phone: 412-383-1675, Fax: 412-647-7951, hok2@upmc.edu.

This study results were in part presented at Conference on Retroviruses and Opportunistic Infections (CROI) 2019.

Conflict of interest: The authors declared no conflicts of interest.

Conclusion: Discontinuation of EFV is not associated with changes in neuropsychological performance or severity of depression in men. Furthermore, we did not observe differences among participants who were never on EFV, continuously on EFV, and on EFV and then switched off.

Keywords

Efavirenz; HIV; neuropsychological function; depression; HIV-associated neurocognitive disorders

Introduction

Efavirenz (EFV)-based antiretroviral therapy (ART) (Tenofovir+ Emtricitabine+ EFV, Atripla®) was a first line ART regimen until 2015 [1]. One of the major concerns for EFV is central nervous system (CNS) toxicity including neurocognitive dysfunction[2], nightmares, and suicidality [3]. Despite this, some people living with HIV in the United States or other developed countries are still on Atripla. Moreover, EFV is still recommended as first-line regimen in low- and middle-income countries by World Health Organization[4]. Although prior studies have focused on EFV and neurocognition, these studies have been cross-sectional and retrospective in nature. For example, in a retrospective study, EFV compared to Lopinavir/ritonavir (LPV/r) use was associated with poorer neurocognitive function (speed of information processing, verbal fluency, and working memory) [2]. In another cross-sectional single-center study, EFV use was associated with four-fold odds of having HIV-associated neurocognitive disorders (HAND) [5]. There is scarce evidence regarding changes in neurocognitive function, suicidality and mood after switching EFV-based regimen to EFV-free regimen. In a recent randomized study, during 48 weeks of follow-up, switching from EFV-based regimen to darunavir/ritonavir-based regimen was associated with improvement in depressive symptoms and sleep quality, but it does not show significant changes in neuropsychological function or quality of life. However, this study recruited only a small number of subjects and had short follow-up period [6]. Another Phase IV open label study involving 16 subjects who switched off EFV showed that discontinuation of EFV was not associated with improvement in neurocognitive function; however, this study is also limited by its small sample size [7]. Given that EFV is still widely used in many low- and middle-income countries as first-line regimen, it was more important to evaluate the impact of EFV switch on neurocognitive effect with longer follow-up and a larger sample size.

Methods

Participants

MACS is a multicenter cohort study enrolling men who have sex with men with HIV infection or at risk of HIV infection. Each participant in the MACS was followed every six months for the assessments of neuropsychological functioning and depressive symptoms and every two years for comprehensive neuropsychological battery [8]. The current study used the following data that were obtained by April 2017 from the MACS. Participants had to have neuropsychological data available in order to be included in this study. This cohort study was conducted with the understanding and the consent of each participant. The

protocols were approved by ethical committee in each study site. Baseline was defined as the time point when the first neuropsychological scores were available.

Participants were prescribed EFV at the discretion of their own health care providers. EFV use is based on self-report during each visit. Participants were divided into three groups. The first group included participants who had never been on EFV (No EFV group). The second group included participants who had been using EFV without switching off (No Switch-OFF group). The third group (Switch-OFF group) included participants who were started on EFV and then were switched off.

Neuropsychological tests and depression scale

The neuropsychological battery included measures of the following cognitive domains, as described in previous studies: Working memory and attention (two indices from a choice reaction time test), Learning (Rey Complex Figure Test - Immediate Recall, Rey Auditory Verbal Learning Test - Sum of Trials 1–5), Motor speed and coordination (Grooved Pegboard), Executive functioning (Trails B, Stroop Interference), Speed of information processing (Symbol Digit Substitution Task, Stroop Color Naming), and Memory (Rey Complex Figure Test - Delayed Recall, Rey Auditory Verbal Learning Test - Delayed Recall) [8]. T-scores were computed for each domain, which were derived from statistical models using normative data from HIV seronegative subjects. For each participant, T-scores were adjusted for age, ethnic group, education level, and number of times the test had been repeated. Then, by averaging all available T-scores in each of the six cognitive domains (for the Motor domain, the lower score of the dominant and non-dominant hand trials of the Grooved Pegboard was used), a summary T-score was reported for each domain. Scores were scaled to be of mean 50 and of standard deviation 10. In case of extreme large or small values, T-scores were truncated below at 10 or above at 90.

In this study, participants were classified as asymptomatic neurocognitive impairment (ANI), minor neurocognitive disorder (MND) and HIV-associated dementia (HAD), according to the Frascati criteria for HIV-associated neurocognitive disorder (HAND) as illustrated in previous report from MACS [8].

Depression was evaluated during follow-up visit by using The Center for Epidemiological Studies Depression (CES-D) score [9]. This score has been validated in HIV population [10, 11]. A total CES-D score summing over all 20 items provides a measure of the severity of depressive symptoms for each subject, ranging from 0 to 60.

Statistical Analysis

In MACS, a participant may have switched on and off EFV multiple times, and his last switch off was included in the analysis. Baseline time point was defined as visits when first neuropsychological data were available.

We performed two analyses. In Analysis 1, we focused on participants who switched off from EFV (Switch-OFF group) and aligned them up at the time of switch (designated the switch point as Time 0) to examine their neuropsychological domain scores and CES-D scores before and after the switch. We set the time frame to be two years before and four

years after switching off from EFV, in order to include enough visits with the NP measures. We used chi square tests for categorical variables, and Kruskal-Wallis rank sum test for continuous variables to compare baseline characteristics between groups. Spaghetti plots were generated for each of six neuropsychological domain scores and the CES-D two years before and four years after the switch point. Lowess smoothing curves were fitted and superimposed on the spaghetti plots. We also fitted linear mixed effects models (LMEMs) to the repeated measures of the six domains of neuropsychological function and the CES-D score to examine the change of each of these seven scores before and after switching. Because some subjects may have multiple measurements before or after the switch, variance originated from repeated measures from the same subject was considered in the LMEMs.

In Analysis 2, participants were classified into three groups as described: No EFV, No Switch-OFF and Switch-OFF. For each group, similar spaghetti plots were created as described in the previous paragraph. However, subjects were aligned at their first visits when neuropsychological scores were available. Multiple points of the same subjects were connected and Lowess smoothing curves were again fitted by neglecting the potential dependence among repeated measures from the same subject. To have better visualization, only three Lowess averaging curves were plotted for each domain score and the CES-D in Figures 2 to illustrate the different patterns in these three EFV groups, and 95% confidence intervals were included.

For neuropsychological domain specific T-scores, it is assumed that they are normally distributed and extreme values are truncated within reasonable ranges (10–90). For CES-D scores, despite that its distribution is right-skewed, the LMEM is rather robust against the departure of normality. Plots and demographics were created in R 3.4.1. LMEMs were fitted in SAS 9.4 (Cary, NC).

Results

Baseline characteristics

This analysis included a total of 1,989 HIV-seropositive participants with neuropsychological data (Table 1) with a median of 3 years of follow up (11,667 person-years). Among them, 1,675 participants had never been on EFV (No EFV), 44 had been on EFV and did not switch off (No Switch-OFF), and 270 were on EFV and later switched off (Switch-OFF). Participants included in this study had a median age of 37 years, and 48.92% had an education level higher or equal to college degree. Median CD4 cell count was 442 cells/μL. 512 participants were on combination ART at baseline and 355 of them had suppressed viral load, with a viral suppression rate 69.33%. Baseline percentage of HAD in No EFV, Switch-OFF, and No Switch-OFF groups were 3.24%, 4.09% and 2.78% (P=0.197). Baseline median CESD scores were 9, 9 and 6 in No EFV, Switch-OFF, and No Switch-OFF groups, respectively (P=0.164).

We also compared participants who were included versus excluded from this study due to lack of neuropsychological data. Those who were included were slightly younger (33.8 vs. 32.1 years), less likely to be Caucasian (69.23% vs. 79.88%), with higher baseline viral suppression rate (19.93 vs. 8.24%) and higher baseline CD4 cell count (585 vs. 546 ml/μL).

Participants also tended to have lower rate of hepatitis C and hepatitis B coinfection rate, recreational drug use rate and alcohol use disorder in inclusion group (Supplementary Table S1).

Analysis 1: Neuropsychological and CES-D scores before and after EFV switch

We evaluated neuropsychological and CES-D score two years prior to and four years after EFV switch in Switch-OFF group. Viral suppression rate at the switch point was 67% and median CD4 cell count was 548 cells/μL. For each neuropsychological domain, mean T scores did not show statistically significant changes over time (Figure 1). Even after stratification by baseline depression level (CES-D score below or above 16), both strata showed similar trends without significant changes in neuropsychological scores (results not shown). We observed similar trends from the CES-D Spaghetti plot (Supplementary Figure S1A). In a sensitivity analysis only including participants with viral suppression prior to EFV switch, neuropsychological scores (Supplementary Figure S2) as well as CES-D scores remained largely stable before and after switch.

We then conducted LMEMs after visual representation, where observations within the same subject were treated as repeated measures and compound symmetric covariance structure was assumed for this. For all six cognitive domains, the T scores before and after EFV switch were all within the range from 40 to 50 and did not show statistically significant differences after switch (Table 2). Similarly, CES-D score did not change significantly after EFV switch (Table 2). In addition, we also did sub-analysis in participants with viral suppression before switch and discovered no significant changes before and after EFV switch (Supplementary Table S2). We also stratified our analysis in Table 2 by different sub-cohorts (enrolled before 2001 vs. after 2001) and did not find any association between cohorts and neuropsychological score changes (results not shown).

Analysis 2: Comparison of neuropsychological and CES-D scores in different groups

We next compared trends in neuropsychological and CES-D scores in the aforementioned three different groups. As shown in Figure 2, neuropsychological scores for different domains did not differ significantly between different groups during follow-up and scores from all groups were oscillating within 50 ±10 range and overlapping 95% confidence intervals. Similarly, CES-D score followed similar patterns in three groups without significant difference. (Supplementary Figure S1B).

Discussion

In this multicenter cohort study of men, we demonstrated that participants on EFV-based regimen did not experience significant changes in their neuropsychological function or depression severity after discontinuation of EFV. Furthermore, trends of neuropsychological function or depression severity were comparable in participants who switched off EFV, continuously on EFV and never on EFV.

In terms of the natural history of HAND, a recent study from MACS revealed that 77% of participants with HAND at baseline remained at the same stage during four years of follow-up. This study indicated that HAND in general is not a progressive process as long as viral

suppression is achieved [8]. However, it has been disputable whether EFV use will alter the progression of neuropsychological deficits. A randomized study conducted by Clifford et al. showed that changes in neuropsychological score were comparable between participants randomized to EFV and non-EFV arms, without statistical significance at any time point during 24 weeks of follow-up [12]; even after extending their observation to 184 weeks, EFV group and non-EFV group had similar changes in neuropsychological score [13]. A small study enrolling 16 subjects demonstrated no significant changes in neurocognitive function after switching EFV to LPV/r-based regimen for 10 weeks, along with brain activity and metabolites (evaluated by proton magnetic resonance spectroscopy and functional magnetic resonance imaging) [7]. These findings are consistent with our analysis. On the contrary, in an early study by Robertson et al., 167 participants who have been on ART for 4.5 years (median) underwent ART interruption; they observed significant improvement in neuropsychological function over 96 weeks and when stratified by EFV use, neuropsychological z scores were improved by 0.67 and 0.96 in non-EFV and EFV groups, respectively, indicating a statistically significant but clinically minor changes. However, in this study, backbone regimens were zidovudine or stavudine, which are currently not first-line regimens [14].

Similarly, severity of depression did not significantly change after EFV discontinuation. A previous randomized crossover study (n=58) involving participants with stable viral suppression on EFV demonstrated that, before and after crossing over EFV with etravirine (ETR), depression, anxiety, sleepiness or sleep quality did not significantly change [15]. This observation is also supported by a recent study in Uganda, in which EFV compared to nevirapine is not associated with increased risk of depression or suicidality[16]. Another earlier randomized trial to compare EFV and non-EFV regimen did not find differences in terms of depression or anxiety [12]. A retrospective study enrolling 281 ART-naïve HIV-positive participants demonstrated that EFV use was not associated with depression after 12-month ART compared to other non-EFV based regimens (adjusted odds ratio 0.9, 95% CI, 0.4–1.8) [17]. Similarly, an analysis from the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales 099 study, a 48-week randomized trial, did not show the association between EFV use (compared with protease-inhibitor) and depression [18]. In contrast, an observational study by Mothapo et al. suggested that EFV discontinuation was associated with improvement in neuropsychiatric performances among symptomatic patients on EFV; however, this study had small sample size (n=23) and this study lacked of comparison arm [19].

Our study has several strengths. First, we were able to compare the trajectories of neuropsychological and CES-D scores before and after EFV discontinuation while many prior studies could only evaluate the trajectories after EFV discontinuation. Second, we were able to compare the neuropsychological and CES-D scores changes in three different groups (No EFV, Switch-OFF, No Switch-OFF) and demonstrated that these three groups had similar trajectories, further supporting our conclusion that EFV use is not associated with neuropsychological and CES-D scores changes. Third, we utilized data from a large, multicenter cohort study with long follow-up duration.

There are a few limitations in this study. First of all, this is a cohort study only including men, which is less suitable for demonstrating causal associations and prone to selection bias. EFV plasma level is unavailable in this analysis, and thus we could not further demonstrate whether EFV level may be associated with changes in neuropsychological or depression scores [20]. We did not have sleep quality data (including vivid dreams, insomnia) available in this analysis, and sleep quality can be affected by EFV use in a dose-dependent manner[20, 21], and previous studies demonstrated that EFV discontinuation was associated with improvement in sleep disturbances [22, 23]. There were only 44 participants in the No Switch-OFF group, and we could not rule out the possibility that this group of people are inherently tolerant of the side effects of EFV. We also did not include single-nucleotide polymorphism (SNP) in the CYP2B6 gene data, which is closely associated with EFV metabolism and its neurotoxicity [24, 25].

In conclusion, we utilized MACS data to demonstrate that EFV discontinuation is not associated with significant changes in neuropsychological performance or depression severity. In addition, participants who remained on EFV had similar neuropsychological performance and depression severity during follow-up when compared with those who were switched off or never on EFV. Our study indicates that it may not be absolutely necessary to switch EFV-based regimen to other regimens due to neuropsychological concerns, especially in people with mild or no baseline neuropsychological symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

We thanked participants in the MACS study. We appreciate assistance from Dr. Benjamin Barrett (Johns Hopkins Bloomberg School of Public Health, Baltimore MD) with data collection and datasheet assembly.

Source of funding:

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS). MACS (Principal Investigators): Johns Hopkins University Bloomberg School of Public Health (Joseph Margolick, Todd Brown), U01-AI35042; Northwestern University (Steven Wolinsky), U01-AI35039; University of California, Los Angeles (Roger Detels, Otoniel Martinez-Maza, Otto Yang), U01-AI35040; University of Pittsburgh (Charles Rinaldo, Lawrence Kingsley, Jeremy Martinson), U01-AI35041; the Center for Analysis and Management of MACS, Johns Hopkins University Bloomberg School of Public Health (Lisa Jacobson, Gypsyamber D'Souza), UM1-AI35043. The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional co-funding from the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH). Targeted supplemental funding for specific projects was also provided by the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute on Deafness and Communication Disorders (NIDCD). MACS data collection is also supported by UL1-TR001079 (JHU ICTR) from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH), Johns Hopkins ICTR, or NCATS. The MACS website is located at http://aidscohortstudy.org/.

References

1. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. Department of Health and Human Services. In; 2017.

2. Ma Q, Vaida F, Wong J, Sanders CA, Kao YT, Croteau D, et al. Long-term efavirenz use is associated with worse neurocognitive functioning in HIV-infected patients. Journal of neurovirology 2016; 22(2):170–178. [PubMed: 26407716]

3. Mollan KR, Smurzynski M, Eron JJ, Daar ES, Campbell TB, Sax PE, et al. Association between efavirenz as initial therapy for HIV-1 infection and increased risk for suicidal ideation or attempted or completed suicide: an analysis of trial data. Annals of internal medicine 2014; 161(1):1–10. [PubMed: 24979445]

4. World Health Organization. Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection Recommendations for a Public Health Approach. Accessed on 1/6/2019. In; 2016.

5. Ciccarelli N, Fabbiani M, Di Giambenedetto S, Fanti I, Baldonero E, Bracciale L, et al. Efavirenz associated with cognitive disorders in otherwise asymptomatic HIV-infected patients. Neurology 2011; 76(16):1403–1409. [PubMed: 21502598]

6. Tiraboschi J, Hamzah L, Teague A, Kulasegaram R, Post F, Jendruleck I, et al. Short Communication: The Impact of Switching from Atripla to Darunavir/Ritonavir Monotherapy on Neurocognition, Quality of Life, and Sleep: Results from a Randomized Controlled Study. AIDS research and human retroviruses 2016; 32(12):1198–1201. [PubMed: 27216134]

7. Payne B, Chadwick TJ, Blamire A, Anderson KN, Parikh J, Qian J, et al. Does efavirenz replacement improve neurological function in treated HIV infection? HIV medicine 2017; 18(9): 690–695. [PubMed: 28247479]

8. Sacktor N, Skolasky RL, Seaberg E, Munro C, Becker JT, Martin E, et al. Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study. Neurology 2016; 86(4): 334–340. [PubMed: 26718568]

9. Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Applied psychological measurement 1977; 1(3):385–401.

10. Privado J, Garrido J. Factorial structure of the Spanish center for epidemiologic studies depression scales in HIV patients. Community mental health journal 2013; 49(4):492–497. [PubMed: 23756721]

11. Chishinga N, Kinyanda E, Weiss HA, Patel V, Ayles H, Seedat S. Validation of brief screening tools for depressive and alcohol use disorders among TB and HIV patients in primary care in Zambia. BMC psychiatry 2011; 11:75. [PubMed: 21542929]

12. Clifford DB, Evans S, Yang Y, Acosta EP, Goodkin K, Tashima K, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. Annals of internal medicine 2005; 143(10):714–721. [PubMed: 16287792]

13. Clifford DB, Evans S, Yang Y, Acosta EP, Ribaudo H, Gulick RM. Long-term impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals (ACTG 5097s). HIV clinical trials 2009; 10(6):343–355. [PubMed: 20133265]

14. Robertson KR, Su Z, Margolis DM, Krambrink A, Havlir DV, Evans S, et al. Neurocognitive effects of treatment interruption in stable HIV-positive patients in an observational cohort. Neurology 2010; 74(16):1260–1266. [PubMed: 20237308]

15. Nguyen A, Calmy A, Delhumeau C, Mercier IK, Cavassini M, Fayet-Mello A, et al. A randomized crossover study to compare efavirenz and etravirine treatment. AIDS (London, England) 2011; 25(1):57–63.

16. Chang JL, Tsai AC, Musinguzi N, Haberer JE, Boum Y, Muzoora C, et al. Depression and Suicidal Ideation Among HIV-Infected Adults Receiving Efavirenz Versus Nevirapine in Uganda: A Prospective Cohort Study. Annals of internal medicine 2018; 169(3):146–155. [PubMed: 29946683]

17. Eaton EF, Gravett RM, Tamhane AR, Mugavero MJ. Antiretroviral Therapy Initiation and Changes in Self-Reported Depression. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2017; 64(12):1791–1794. [PubMed: 28419238]

18. Journot V, Chene G, De Castro N, Rancinan C, Cassuto JP, Allard C, et al. Use of efavirenz is not associated with a higher risk of depressive disorders: a substudy of the randomized clinical trial ALIZE-ANRS 099. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2006; 42(12):1790–1799. [PubMed: 16705588]

19. Mothapo KM, Schellekens A, van Crevel R, Keuter M, Grintjes-Huisman K, Koopmans P, et al. Improvement of Depression and Anxiety After Discontinuation of Long- Term Efavirenz Treatment. CNS & neurological disorders drug targets 2015; 14(6):811–818. [PubMed: 25808896]

20. Gutierrez F, Navarro A, Padilla S, Anton R, Masia M, Borras J, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 2005; 41(11):1648–1653. [PubMed: 16267739]

21. Mukonzo JK, Okwera A, Nakasujja N, Luzze H, Sebuwufu D, Ogwal-Okeng J, et al. Influence of efavirenz pharmacokinetics and pharmacogenetics on neuropsychological disorders in Ugandan HIV-positive patients with or without tuberculosis: a prospective cohort study. BMC infectious diseases 2013; 13:261. [PubMed: 23734829]

22. Ward DJ, Curtin JM. Switch from efavirenz to nevirapine associated with resolution of efavirenz-related neuropsychiatric adverse events and improvement in lipid profiles. AIDS patient care and STDs 2006; 20(8):542–548. [PubMed: 16893323]

23. Scourfield A, Zheng J, Chinthapalli S, Waters L, Martin T, Mandalia S, et al. Discontinuation of Atripla as first-line therapy in HIV-1 infected individuals. AIDS (London, England) 2012; 26(11): 1399–1401.

24. Pinillos F, Dandara C, Swart M, Strehlau R, Kuhn L, Patel F, et al. Case report: Severe central nervous system manifestations associated with aberrant efavirenz metabolism in children: the role of CYP2B6 genetic variation. BMC infectious diseases 2016; 16:56. [PubMed: 26831894]

25. Gandhi M, Greenblatt RM, Bacchetti P, Jin C, Huang Y, Anastos K, et al. A single-nucleotide polymorphism in CYP2B6 leads to >3-fold increases in efavirenz concentrations in plasma and hair among HIV-infected women. The Journal of infectious diseases 2012; 206(9):1453–1461. [PubMed: 22927450]

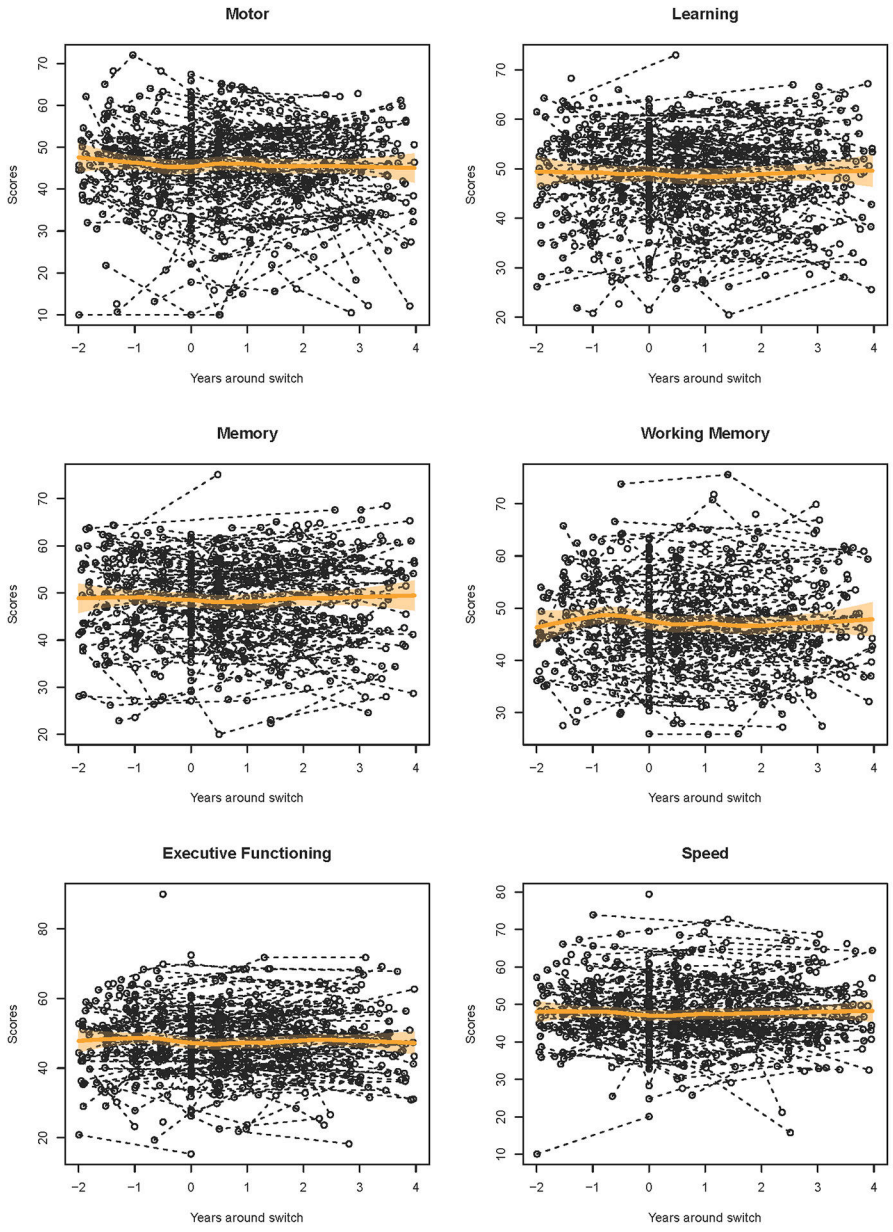

Figure 1.

Scores of six neuropsychological domains before and after switching off Efavirenz (95% confidence intervals included).

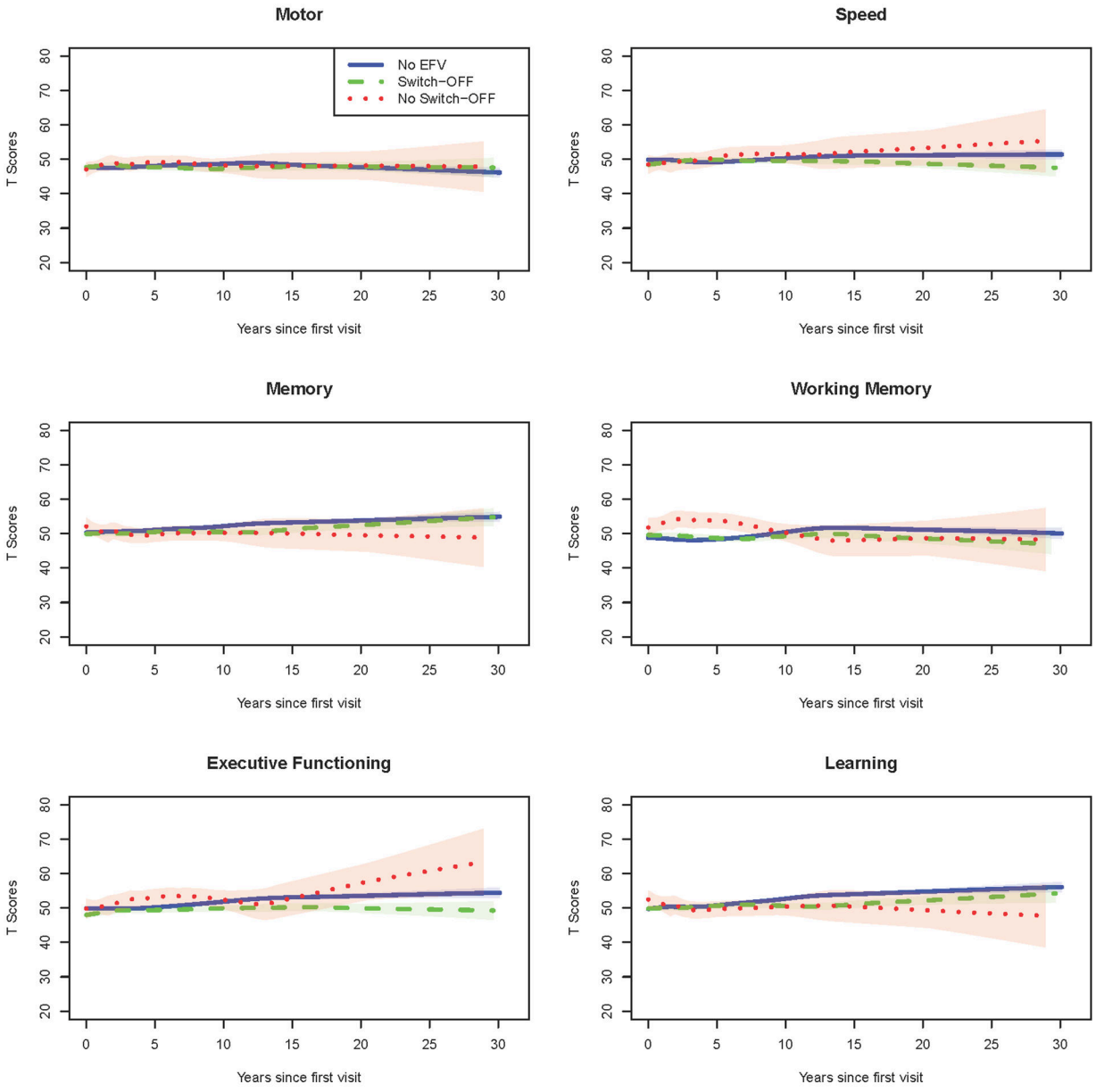

Figure 2.

Longitudinal comparison of neuropsychological scores in No EFV, Switch-OFF, and No Switch-OFF groups (95% confidence intervals included).

AIDS. Author manuscript; available in PMC 2020 July 01.

Table 1

Baseline characteristics. For variables with missing data, total number of available data (N) will be noted in the table.

	Total Population (N=1,989)	No EFV (N=1,675)	Switch-OFF (N=270)	No Switch-OFF (N=44)	P value
Age, median year (IQR)	37 (32, 43)	37 (32, 43)	39 (32, 45)	39 (33, 46)	0.0067
Ethnicity, n (%)					<0.0001
Caucasian	1,377 (69.23%)	1,220 (72.84%)	133 (49.26%)	24 (54.55%)	
Other	612 (30.77%)	455 (27.16%)	137 (50.74%)	20 (45.45%)	
Education≥ college degree, n (%)	973 (48.92%)	833 (49.73%)	120 (44.44%)	20 (45.45%)	0.245
CD4 cell count, median (IQR)	442 (246, 662) N=1,983	413 (221, 643) N=1,669	527 (346, 736) N=270	576 (411, 774) N=44	<0.0001
Plasma HIV RNA, %undetectable (<50 copies/ml)	415 (22.90%) N=1,812	274 (18.29%) N=1,498	114 (42.22%) N=270	27 (61.36%) N=44	<0.0001
Plasma HIV RNA, %undetectable in participants on combination ART (<50 copies/ml)	355 (69.33%) N=512	228 (67.46%) N=338	103 (70.55%) N=146	24 (85.71%) N=28	0.12
Hepatitis C coinfection, n (%)	196 (10.04%) N=1,953	156 (9.50%) N=1,642	36 (13.43%) N=268	3 (9.30%) N=43	0.137
Hepatitis B coinfection, n (%)	123 (6.29%) N=1,957	99 (6.01%) N=1,646	20 (7.49%) N=267	4 (9.09%) N=44	0.914
Hypertension, n (%)	146 (7.34%)	98 (5.85%)	41 (15.19%)	7 (15.91%)	<0.0001
Dyslipidemia, n (%)	505 (70.83%) N=713	352 (71.69%) N=491	126 (67.74%) N=186	27 (75.00%) N=36	0.512
Diabetes, n (%)	48 (2.41%) N=690	33 (1.97%) N=466	11 (4.07%) N=187	4 (9.09%) N=37	0.551
Illicit drug use, n (%)	1,453 (73.98%) N=1,964	1,272 (76.72%) N=1,658	162 (61.36%) N=264	19 (45.24%) N=42	<0.0001
Alcohol use >3 drinks/week, n (%)	743 (37.41%) N=1,986	626 (37.44%) N=1,672	100 (37.04%) N=270	17 (38.64%) N=44	0.978
Neurocognitive function, T score (IQR)					
Executive function	50.0 (43.3, 55.7) N=1,943	50.2 (43.5, 55.9) N=1,629	48.5 (42.0, 54.5) N=270	49.7 (43.3, 55.9) N=44	0.035
Speed of information processing	49.1 (43.2, 55.1) N=1,988	49.3 (43.4, 55.3) N=1,674	48.0 (43.0, 54.5) N=270	49.6 (42.8, 52.6) N=44	0.100
Attention and working memory	48.3 (42.8, 55.1) N=1,761	48.0 (42.6, 55.0) N=1,453	49.4 (43.7, 55.2) N=265	51.1 (46.4, 56.7) N=43	0.063
Learning	49.7 (43.1, 55.8) N=1,976	49.8 (43.2, 55.8) N=1,662	49.0 (42.7, 55.7) N=270	51.4 (44.7, 58.6) N=44	0.618

	Total Population (N=1,989)	No EFV (N=1,675)	Switch-OFF (N=270)	No Switch-OFF (N=44)	P value
Memory	50.8 (43.3, 56.4) N=1,974	49.7 (43.5, 55.4) N=1,660	49.9 (43.6, 56.0) N=270	53.1 (44.6, 58.1) N=44	0.287
Motor	47.5 (40.7, 53.4) N=1,985	47.5 (41.45, 53.4) N=1,671	48.1 (39.7, 53.6) N=270	46.1 (43.3, 50.5) N=44	0.839
HAND					0.197
ANI	128 (15.78%) N=811	99 (17.84%) N=555	25 (11.36%) N=220	4 (11.11%) N=36	
MND	114 (14.06%) N=811	73 (13.15%) N=555	38 (17.27%) N=220	3 (8.33%) N=36	
HAD	28 (3.45%) N=811	18 (3.24%) N=555	9 (4.09%) N=220	1 (2.78%) N=36	
CES-D score (IQR)	9 (4, 19) N=1,917	9 (4, 19) N=1,611	9 (3.5, 20) N=263	6 (1.5, 14.5) N=43	0.164

EFV, efavirenz; TIA, transient ischemic attack; IQR, interquartile range; HAND, HIV-associated neurocognitive disorder; ANI, asymptomatic neurocognitive impairment; MND, minor neurocognitive disorder; HAD, HIV-associated dementia; CES-D, Center for Epidemiologic Studies Depression Scale

AIDS. Author manuscript; available in PMC 2020 July 01.

Table 2.

Neuropsychological and CES-D mean scores before and after EFV switch (with 95% confidence intervals).

	n	Mean before switch		Mean after switch		P Value
Neuropsychological scores						
Motor	220	45.08	(43.28,46.88)	43.97	(42.49,45.45)	0.16
Speed	221	48.68	(47.28,50.07)	48.36	(47.16,49.56)	0.56
Memory	221	49.32	(47.91,50.73)	48.63	(47.42,49.84)	0.22
Working memory	215	47.97	(46.47,49.47)	47.54	(46.31,48.78)	0.51
Executive functioning	221	47.97	(46.40,49.55)	47.97	(46.60,49.34)	0.99
Learning	221	49.40	(47.93,50.87)	48.69	(47.44,49.94)	0.24
Depression score						
CES-D	218	15.08	(13.15,17.01)	13.72	(12.12,15.33)	0.11

All are modelled separately. Confident intervals are of 95%

EFV, efavirenz; CES-D, Center for Epidemiologic Studies Depression Scale.